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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/550,985	09/26/2005	Daria Onichtchouk	18744-0033	4668

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EXAMINER	
SGAGIAS, MAGDALENE K	
ART UNIT	**PAPER NUMBER**
1632	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/550,985	ONICHTCHOUK ET AL.	
	Examiner	Art Unit	
	Magdalene K. Sgagias	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 September 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *37-63,83 and 84* is/are pending in the application.

4a) Of the above claim(s) *46-63* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *37-45 and 83-84* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's arguments filed 9/13/07 have been fully considered but they are not persuasive. The amendment has been entered. Claims 37-63, 83-84 are pending. Claims 46-63 are withdrawn. Claims 1-36, 64-82 are canceled. Claims 37-45 and 83-84 are under consideration.

Claim Objections

Claim 37 objection because of the following informalities: Claim recites "The use". The article "The" should be replaced by "A" is withdrawn.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 37, 39, 40, 83 are rejected under 35 U.S.C. 102(**b**) as being anticipated by **Blyszczuk et al,** (PNAS) 100(3): 998-1003, February 4, 2003).

Blyszczuk et al, teach a modulator/effector to promote development of insulin producing cells comprising administering to mouse embryonic stem cells vector encoding pax4, which is a a modulator/effector thereof, as recited in the claims since it is a - pancreatic gene under the control of the human CMV early/promoter region and promotes differentiation of progenitor cell into insulin producing cells (p 998 under material and methods and p 999, 2nd column under results) (**claims 37, 40, 83**).

Blyszczuk et al, teach the pax4 positive differentiated insulin producing cells wee beta cells as shown by immunofluorescence and electromicroscopical studies figure 4 and p 1002, 1st column, 1st paragraph) (**claim 38**).

Blyszczuk et al, teach the insulin producing cells are of mammalian origin since said cells are mouse embryonic cells (**claim 39**).

Thus, **Blyszczuk et al,** anticipate claimed invention.

This rejection is set forth under 102(b) because applicants have not met the conditions for obtaining the benefit of the earlier filing date. If Applicants submit the EPO 03006948.8 03/26/2003, the rejection would still stand under 102(a).

Claims **1, 84** are rejected under 35 U.S.C. 102(b) as being anticipated by **Rabinovitch, et al,** (Diabetes, 48: 1223-1229, 1999).

Rabinovitch, et al, teach the transfection of human pancreatic islet cells with the bcl2 gene and the transfected beta cells with the bcl2 gene as a modulator secreted insulin (p 1226 and figure 3) (**claims 1, and 84**).

Thus, **Rabinovitch, et al,** anticipate claimed invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 37-45 and 83-84 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims are drawn to a use of a saposin-related product and/or a modulator/effector thereof, to promote development of insulin producing cells comprising administering to the cell an effective amount of asaposin-related product and/or a modulator effector thereof. Embodiments limit insulin producing cells into beta cells or transfected with a pancreatic gene, or pax4 gene. Embodiments limit the use for the treatment of a disease associated with impaired beta-cell function, diabetes type I, diabetes type II or LADA. Embodiments limit the saposin-related product or a modulator/effector thereof that influences the expression level or function of a saposin-related product is administered to a patient as a pharmaceutical composition e.g. enterally, parenterally or topically directly to the pancreas. Embodiments limit the insulin producing cells have been transfected with the Pax4 gene or wherein the insulin producing cells are of human origin.

The specification teaches the induction of differentiation of insulin-producing cells by prosaponin in vitro after exposure of mouse embryonic stem (ES) cells (embryoid bodies) tranduced with the Pax4 gene to the prosaponin (specification examples 10 and 11). The specification also contemplates the therapeutic potential of prosaposin induced insulin-producing cells to improve and cure diabetes can be investigated by transplanting the cells into streptozotocin induced diabetic mice (specification p 64, lines 15-16, example 12). However, the specification has failed to provide guidance to correlate a use of induction of differentiation of insulin-producing cells by prosaponin in vitro to administering in vivo an effective amount of said saposin-related product and/or effector thereby promoting development of insulin producing cells in vivo or treating a disease associated with a type of diabetes in a patient by any route of administration of said saposin-related product and/or modulator/effector. It would have required undue experimentation to make and use the claimed invention without a reasonable expectation of success.

The claims embrace the administration to cells of an effective amount of a saposin-related product and/or modulator/effector to promote development insulin producing cells in vivo and embodiments limit, wherein the insulin producing cells have been transfected with the Pax4 gene in vivo. The art teaches that tissue regeneration and restoration of normal tissue function is a major problem in autoimmune diseases like type I diabetes (**Chernajovsky et al,** Nature Reviews, 4: 1-12, 2004) (p 2, 2nd column, last paragraph). Chernajovsky et al, notes that strategies to treat type I diabetes such as surrogate beta cells, have limitations due to the immunogenicity of transgenes and vectors and fate of engineered cells in vivo (p 10, 1st column, 1st paragraph). Chernajovsky further discusses that "A current limitation of most preclinical studies of treatments for autoimmune disease is that immunogenic vectors are often used as proof of concept in animal models. Progress has also been restricted because many studies are short term (in part due to the vector) or have used an acute model of disease, which does not truly reflect the chronic nature of autoimmune diseases in humans. Yet these studies, using numerous targets, have provided strong evidence that local or systemic gene therapy could be a potent method of treatment and warrants further investigation (p 10, 2nd column, 1st paragraph). **Jun et al** (Current Gene Therapy, 5: 249-262, 2005) even after the filing of the instant application notes that studies for regulating the growth and differentiation of islet cells have identified many transcription factors such as Pax4 may play a role in pancreatic development (p 254, 1st column, 1st paragraph), however, there is no satisfactory strategy yet for clinical application to human type 1diabetes (p 254, 2nd column 2nd paragraph). Jun went on to say that more studies are required for the identification and isolation of beta cell progenitor and/or stem cells, promotion of the proliferation of regenerated or differentiated insulin-producing beta cells, and prevention of immune attack against new beta cells (p 254, 2nd column, 2nd paragraph). Jun concludes that Insulin gene therapy is limited by appropriate

insulin production in response to physiological levels of glucose. βcell regeneration is limited by persisting autoimmune attack against newly generated βcells. None of these approaches have yet provided the perfect solution for the cure of type 1 diabetes and are still "work in progress." It is hoped that continuous effort on a variety of potential approaches will offer the best choices for the permanent cure of human type 1 diabetes (p 257, 1st column. Jun also reports even though embryonic stem cells transfected with Pax4 gene, a transcription factor essential for beta cell development and differentiation into insulin-producing cells and normalized blood glucose when transplanted into diabetic mice, however, the report by **Rajagopal et al,** (Science, 299: 363, 2003) does not support beta cell differentiation from embryonic stem cells. Rajagopal reports that differentiated insulin-positive cells were reported to contain 1 μg of insulin per mg of total protein. This is less than 0.02% of the insulin found in the media to which these cells are exposed, raising the possibility that insulin is subsequently cultured in insulin-deficient media lost insulin staining. (This release of absorbed insulin may mimic genuine secretion.) Some absorbed insulin is retained for more than 3 weeks in insulin-deficient media. Therefore, the mere persistence of insulin immunoreactivity in a transplant of ES cell progeny is insufficient evidence of βcell differentiation or function (P 363, 1st column last paragraph bridge 2nd column).

The specification contemplates the transplantation of Pax4 ES derived insulin producing cells in STZ diabetic mice for therapeutic potential of prosaposin induced insulin-producing cells to improve and cure diabetes can be investigated (p 64, example 12). **Narang et al,** (Pharmacological reviews, 58(2): 194-243, 2006) notes that:

"Upon subcutaneous implantation in streptozotocininduced diabetic mice, ES cells vascularized, formed aggregates similar to pancreatic islets, and remained insulin positive, although a sustained correction of hyperglycemia **was not observed** (Lumelsky et al., 2001). Researchers sought to overcome the low capacity of insulin storage and secretion by these cells by using growth inhibitors (Blyszczuk et al., 2003) and by stable

expression of the *Pax4* gene (Blyszczuk et al., 2003), which is a transcription factor essential for β-cell differentiation during embryonic development (Soria, 2001). There have also been observations and **arguments against** using nestin-positive cells as β-cell progenitors (Lendahl et al., 1990; Selander and Edlund, 2002), as well **as using insulin immunoreactivity as a marker of β-cell phenotype** (Rajagopal et al., 2003). Furthermore, cell therapy of diabetes requires several considerations, such as control of cell number and cell differentiation in vivo and protection from host immune response. Immune protection of transplanted cells has been attempted by immunoisolation, induction of donor-specific tolerance, and genetic manipulations of donor cells to resist immune attack (Efrat, 1999)." (p 215, 1st column, 1st paragraph).

While progress has been made in recent years for in vivo gene transfer, vector targeting in vivo to be desired organs continued to be unpredictable and inefficient. For example, numerous factors complicate the gene delivery art that could not have been overcome by routine experimentation. These include, the fate of DNA vector itself, volume of distribution, rate of clearance in tissue, the in vivo consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of RNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced (Ecke et al , Goodman & Gilman's The Pharmacological basis of Therapeutics, McGraw-Hill, New York, NY. pp 77-101).

The instant specification does not provide any relevant teachings, specific guidance, or working examples for overcoming the limitations of beta cell differentiation from embryonic stem cells in vivo, targeting a saposin-related product and/or a modulator/effector in cells in vivo to promote development of insulin producing cell by administering to the cells in vivo an effective amount of a saposin-related product and/or a modulator/effector by any and all routes of administration for treating any type of diabetes as raised by the state of the art. Therefore, the

skilled artisan would conclude that the state of art of promoting the development of insulin producing cells in vivo by a saposin-related product and/or a modulator/effector is undeveloped and unpredictable at best. Given the lack of guidance provided by the instant specification, it would have required undue experimentation to practice the invention as claimed for promoting the development of insulin producing cells in vivo by a saposin-related product and/or a modulator/effector without a reasonable expectation of success.

Therefore, in view of the quantity of experimentation necessary to determine the parameters listed above for the beta cell differentiation from embryonic stem cells by administering to the cells in vivo an effective amount of a saposin-related product and/or a modulator/effector, to promote development of insulin producing cells resulting in the treatment of a type of diabetes, the lack of direction or guidance provided by the specification for the beta cell differentiation from embryonic stem cells by administering to the cells in vivo an effective amount of a saposin-related product and/or a modulator/effector, to promote development of insulin producing cells resulting in the treatment of a type of diabetes, the absence of working examples that correlate to the beta cell differentiation from embryonic stem cells by administering to the cells in vivo an effective amount of a saposin-related product and/or a modulator/effector, to promote development of insulin producing cells resulting in the treatment of a type of diabetes, the unpredictable state of the art with respect to beta cell differentiation from embryonic stem cells by administering to the cells of a patient in need thereof an effective amount of a saposin-related product and/or a modulator/effector, particularly type I/II diabetes or LADA , and the breadth of the claims directed to all types and stages of diabetes, it would have required undue experimentation for one skilled in the art to make and/or use the claimed invention.

Applicants argue the Examiner cites certain prior art and non-prior art references for the general proposition that clinical applications for treatments of insulin producing cells are not fully developed and "have not yet provided the perfect solution." However, all that is required for patentability is that applicants enable a credible and relevant utility for the invention. A novel mechanism for the promotion of insulin producing cells has been defined herein. Applicants have certainly enabled a very useful and valuable research tool, such as for drug screening, through its demonstration of the saposin-related induction of insulin producing cells of the present invention. Applicants also state for the record that the invention does provide a demonstration convincing to one skilled in the art that the saposin-related induction of insulin producing cells would be likely to provide some therapeutic benefit to patients, despite the need for more detailed clinical experimentation and optimization for FDA approval, and the claims are intended to encompass such uses as well.

These arguments are not persuasive because applicants have not provided evidence to overcome the issue of promoting development of insulin producing cells in vivo by administering to the cells in vivo an effective amount of a saposin-related product and/or a modulator/effector resulting in the treatment of a type of diabetes. The MPEP only states the examiner cannot ask for clinical trial data regarding safety or efficacy for enablement. No such requirement is in the present record. Applicants claims encompass an effective amount of a saposin-related product and/or a modulator/effector resulting in the treatment of a type of diabetes by an effective amount of a saposin-related product and/or a modulator/effector resulting in the treatment of a type of diabetes. Applicants have not shown such an effect in vivo. There is no enabled use for no effect.

The courts have stated that "tossing out the mere germ of an idea does not constitute enabling disclosure." Genentech, 108 F.3d at 1366 (quoting Brenner v. Manson, 383 U.S. 519,

536 (1966) (stating, in context of the utility requirement, that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion")). "[R]easonable detail must be provided in order to enable members of the public to understand and carry out the invention." Id. In the instant case, such reasonable detail is lacking. The specification provides no guidance on how to use the compounds of claim 37 as beta-cell growth factors.

15. See Rasmusson v. SmithKline Beecham Corp., 75 USPQ2d 1297 (CA FC 2005) which teaches: "If mere plausibility were thetest for enablement under section 112, applicants could obtain patent rights to "inventions" consisting of little more than respectable guesses as to the likelihood of their success. When one of the guesses later proved true, the "inventor" would be rewarded the spoils instead of the party who demonstrated that the method actually worked. That scenario is not consistent with the statutory requirement that the inventor enable an invention rather than merely proposing an unproved hypothesis.".

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Magdalene K. Sgagias whose telephone number is (571) 272-3305. The examiner can normally be reached on Monday through Friday from 9:00 am to 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras, Jr., can be reached on (571) 272-4517. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

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